REMARKS

Prior to the present amendment, claims 19-28 were pending. By this amendment, Applicants have amended claim 19 by incorporating the limitation of dependent claim 20, and cancelled claims 20, 24 and 27. Accordingly, claims 19, 21-23, 25, 26, and 28 are currently pending.

The Invention

The present invention provides a real time (e.g. results in less than thirty minutes) insulin test system that has at least one photomultiplier detector and at least one reservoir. The reservoir has (i) monoclonal anti-insulin or anti-C peptide capture antibodies coated onto the surface of the reservoir, and (ii) monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer present in the reservoir in dried form. The reservoir receives a sample and a wash solution. The labeled antibodies allow for photometrical detection.

Rejection Under 35 U.S.C. §112

Claim 27 has been rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In response, Applicants have cancelled claim 27. Therefore, Applicants respectfully submit that the rejection of claim 27 has been rendered moot.

Rejection Under 35 U.S.C. §103 over Nakanome et al. in view of Landa et al.

Claims 19, 22, 27 and 28 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Nakanome et al. (*Biomedical Research* 18(5), 389-393, 1997) in view of Landa et al. (U.S. Patent No. 4,626,684).

Applicants note that the Examiner did not reject dependent claim 20 under 35 U.S.C. §103(a) over Nakanome et al. in view of Landa et al. Claim 20 recites that the monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer are present in the reservoir in dried form. Importantly, neither Nakanome nor Landa disclose or suggest a test system where the antibodies (e.g. monoclonal anti-insulin or anti-C peptide) useful as a tracer are present in the reservoir in dried form.

In response to this rejection, and in the interest of moving the application towards allowance, Applicants have amended independent claim 19 by incorporating the limitation recited in dependent claim 20.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

Applicants have demonstrated the importance of the monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer being present in the reservoir in dried form. Upon combining Nakanome et al. and Landa et al., all of the claim limitations are not disclosed or suggested.

Accordingly, Applicants respectfully submit that amended claim 19 is patentable over Nakanome et al. in view of Landa et al. In addition, dependent claims 22, 27 and 28 should also be patentable over Nakanome et al. in view of Landa et al. at least for the same reasons that claim 19 is patentable.

Therefore, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 19, 22, 27 and 28 under 35 U.S.C. §103(a) based on Nakanome et al., in view of Landa et al.

Rejection Under 35 U.S.C. §103 over Nakanome et al. and Landa et al. in view of Milford et al.

Claim 20 has been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Nakanome et al. and Landa et al., in view of Milford et al. (U.S. Patent No. 4,517,289). The Examiner recognizes that Nakanome et al. and Landa et al. differ from the claimed invention by failing to teach the labeled monoclonal anti-insulin antibody present in dried form.

According to the Examiner, Milford et al. disclose the use of lyophilized monoclonal antibodies. The Examiner further asserts that it would have been obvious to one of skill in the art to incorporate the use of lyophilized antibodies as taught by Milford et al. into the modified device of Nakanome et al. Applicants respectfully disagree.

First, Nakanome et al. disclose an assay for measuring pro-insulin. In fact, in the Abstract, Nakanome et al. state that their assay is specific for proinsulin, and failed to detect both insulin and C-peptide. In contrast, the claimed invention is an assay kit for detecting insulin. Therefore, the assay of Nakanome et al. differs from the claimed invention.

Furthermore, the assay disclosed in Nakanome et al. requires a lengthy incubation period. Page 390, column 1 states the following:

> In each well, proinsulin standard or diluted serum (100 μl) were mixed. After incubation for **18 h** at 4°C, each well was washed 3 times with washing solution and biotin-labelled antibody (100 μl) was added. The mixture was then incubated for **18 h** at 4°C and the washing procedure was repeated. Streptavidin-peroxidase conjugate was diluted with 0.01 M phosphate buffer, pH 7.2, containing 0.15 M NaCl, 10% (v/v) normal goat serum and 10% (w/v)

> polyethylene glycol (PEG) 6000. Diluted streptavidin-peroxidase conjugate (100 µl) was added to each well and the plate was incubated in the dark at room temperature for **1 h**. The washing procedure was repeated and 100 µl of enzyme substrate (1,2 phenylenediamine/H_2O_2) were added to each well. After incubation in the dark at room temperature for **0.5 h**, the enzymatic reaction was stopped with 100 µl of 1N H_2SO_4 per well. *(Emphasis added)*

Therefore, Nakanome et al. disclose an assay which requires at least 37.5 hours. In contrast, as explained above, by including the monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form, substantial time is saved in carrying out the test.

For example, results become available in less than thirty (30) minutes. See page 6, lines 6-10 of the specification as originally filed. Accordingly, the claimed invention differs from the assay disclosed in Nakanome et al.

Landa et al. merely disclose a fluorescence analyzer. Nowhere in Landa et al. is there any disclosure or suggestion of a real-time assay to measure insulin levels using monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form.

Milford et al. discloses at column 8, lines 65 et seq., that their kit can contain HLA antibodies in lypholized form, as well as other reagents and accessories, such as a reaction vessel. Therefore, Milford et al. disclose that the antibody in lyophilized form and the reaction vessel are two separate components of the kit.

Nowhere in Milford et al. is there any disclosure or suggestion that the antibodies are present in dried form in a reaction reservoir. In addition, nowhere in Milford et al. is there any

disclosure or suggestion of using anti-insulin or anti-C peptide antibodies in such a test system. Thus, Milford et al. does not disclose or suggest the claimed invention.

In fact, Milford et al. teach away from the claimed invention. As stated above, Milford et al. disclose that the antibody in lyophilized form and reaction vessel are two separate components of the kit. In contrast to Milford et al., the claimed invention contains a reservoir with the monoclonal antibodies useful as a tracer present in dried form in the reservoir. Thus, in the claimed invention, the reservoir and dried antibody useful as a tracer are not two separate components of the kit.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

Upon combining the teachings of Nakanome et al., Landa et al., and Milford et al., all of the claim limitations are neither taught nor suggested. Importantly, there is a lack of motivation in any of the cited references to combine teachings. Even upon combining teachings, one would not arrive at the present invention.

Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Nakanome et al. and Landa et al., in view of Milford et al. Accordingly, Applicants respectfully request reconsideration of the above §103 rejection.

Rejection Under 35 U.S.C. §103 over Nakanome et al. and Landa et al. in view of Campbell et al.

Claim 21 has been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Nakanome et al., and Landa et al., in view of Campbell et al. (U.S. Patent No. 4,946,958). The

Examiner recognizes that Nakanome et al., and Landa et al. differ from the instant invention in failing to teach the label being a chemiluminescent label.

According to the Examiner, Campbell et al. disclose a chemiluminescent label linked to a monoclonal antibody. The Examiner further asserts that it would be obvious to one skilled in the art to incorporate the chemiluminescent label of Campbell in the method of Nakanome et al., and arrive at the claimed invention.

As discussed above, Nakanome et al. discloses an assay for measuring pro-insulin that requires a lengthy incubation period, for example, at least 37.5 hours, and does not disclose using monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form. Landa et al. merely discloses a fluorescence analyzer.

Campbell et al. discloses a compound that is useful as a chemiluminescent label that can be linked to a monoclonal antibody.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

Applicants have demonstrated the importance of using monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form, in the test system.

Upon combining the teachings of Nakanome et al., and Landa et al., in view of Campbell et al., all of the claim limitations are neither taught nor suggested. Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Nakanome et al., and Landa et al., in view of Campbell et al.

Importantly, there is a lack of motivation in any of the cited references to combine teachings. Even upon combining teachings, one would not arrive at the present invention.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the above §103 rejection.

Rejection Under 35 U.S.C. §103 over Nakanome et al. and Landa et al. in view of Schulz et al.

Claims 23 and 26 have been rejected under 35 U.S.C. §103(a) as allegedly being obvious over Nakanome et al. and Landa et al., in view of Schulz et al., Band 68 Heft 3, pp.309-318 (1976) (abstract only in English). The Examiner recognizes that Nakanome et al. and Landa et al. differ from the claimed invention in failing to teach obtaining a sample by a probe arranged to be introduced into the Vena porta.

The Examiner contends that because Schulz et al. discloses obtaining a sample by insertion of a catheter in the *Vena porta*, it would have been obvious to one of ordinary skill in the art to obtain a sample as taught by Schulz et al. for use in the method of Nakanome et al. and Landa et al., and arrive at the claimed invention. Applicants respectfully disagree.

As discussed at length above, the present invention is for a test system that measures insulin levels and produces results in a short period of time, using monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form. As recited in claims 23 and 26, the claimed test system utilizes a sample obtained by a probe arranged to be introduced in the *Vena splenica* and/or *Vena porta*.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

As discussed above, Nakanome et al. and Landa et al. fail to disclose or suggest a crucial component of the claimed test system, namely, monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form.

Upon combining the teachings of Nakanome et al., and Landa et al., in view of Schultz et al., all of the claim limitations are neither taught or suggested.

Importantly, there is a lack of motivation in any of the cited references to combine teachings. Even upon combining teachings, one would not arrive at the present invention.

Therefore, based on the foregoing discussion, Applicants' claimed invention is not obvious over Nakanome et al., and Landa et al., in view of Schultz et al. Accordingly, Applicants respectfully request reconsideration and withdrawal of the above §103 rejection.

Rejection Under 35 U.S.C. §103(a) over Nakanome et al. and Landa et al. in view of Milford et al. and further in view of Schultz et al.

Claim 24 has been rejected under 35 U.S.C. §103(a) over Nakanome et al. and Landa et al., in view of Milford et al., and further in view of Schultz et al. As discussed at length above, Applicants have provided arguments refuting the disclosure of Nakanome et al. and Landa et al. in view of Milford et al. Also, as discussed above, Schultz et al. merely discloses obtaining a sample by insertion of a catheter in the *Vena porta*.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

As discussed above, Nakanome et al. and Landa et al. in view of Milford et al. fail to disclose or suggest a crucial component of the claimed test system, namely monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form.

Upon combining the teachings of Nakanome et al. and Landa et al. in view of Milford et al. and further in view of Schultz et al., all of the claim limitations are neither taught or suggested.

Importantly, there is a lack of motivation in any of the cited references to combine teachings. Even upon combining teachings, one would not arrive at the present invention.

Accordingly, Applicants' claimed invention cannot be obvious over Nakanome et al., Landa et al., in view of Milford et al., and further in view of Schultz et al. Accordingly, Applicants respectfully request reconsideration and withdrawal of the above §103 rejection.

Rejection Under 35 U.S.C. §103(a) over Nakanome et al. and Landa et al. in view of Campbell et al. and further in view of Schultz et al.

Claim 25 has been rejected under 35 U.S.C. §103(a) over Nakanome et al. and Landa et al., in view of Campbell et al., and further in view of Schultz et al. As discussed at length above, Applicants have provided arguments refuting the disclosure of Nakanome et al. and Landa et al. in view of Campbell et al. Also, as discussed above, Schultz et al. merely discloses obtaining a sample by insertion of a catheter in the *Vena porta*.

In order to establish a *prima facie* case of obviousness, one of the criteria to be met is that the prior art references, when combined, must teach or suggest all of the claim limitations. See MPEP §2142.

As discussed above, Nakanome et al. and Landa et al. in view of Campbell et al. fail to disclose or suggest a crucial component of the claimed test system, namely monoclonal anti-insulin or anti-C peptide antibodies useful as a tracer in the reservoir in dried form.

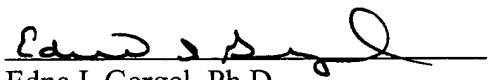
Upon combining the teachings of Nakanome et al. and Landa et al. in view of Campbell et al. and further in view of Schultz et al., all of the claim limitations are neither taught or suggested.

Importantly, there is a lack of motivation in any of the cited references to combine teachings. Even upon combining teachings, one would not arrive at the present invention.

Accordingly, Applicants' claimed invention cannot be obvious over Nakanome et al., Landa et al., in view of Campbell et al., and further in view of Schultz et al. Accordingly, Applicants respectfully request reconsideration of the above §103 rejection.

In view of the above amendments and remarks, Applicants respectfully submit that the application is now in condition for allowance. If the Examiner believes a telephone discussion with the Applicants' representative would be of assistance, he is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



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